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Pooled Analysis of Prospective Cohort Studies on Height, Weight, and Breast Cancer Risk

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The association between anthropometric indices and the risk of breast cancer was analyzed using pooled data from seven prospective cohort studies. Together, these cohorts comprise 337,819 women and 4,385 incident invasive breast cancer cases. In multivariate analyses controlling for reproductive, dietary, and other risk factors, the pooled relative risk (RR) of breast cancer per height increment of 5 cm was 1.02 (95% confidence interval (CI): 0.96, 1.10) in premenopausal women and 1.07 (95% CI: 1.03, 1.12) in postmenopausal women. Body mass index (BMI) showed significant inverse and positive associations with breast cancer among pre- and postmenopausal women, respectively; these associations were nonlinear. Compared with premenopausal women with a BMI of less than 21 kg/m^2, women with a BMI exceeding 31 kg/m^2 had an RR of 0.54 (95% CI: 0.34, 0.85). In postmenopausal women, the RRs did not increase further when BMI exceeded 28 kg/m^2; the RR for these women was 1.26 (95% CI: 1.09, 1.46). The authors found little evidence for interaction with other breast cancer risk factors. Their data indicate that height is an independent risk factor for postmenopausal breast cancer; in premenopausal women, this relation is less clear. The association between BMI and breast cancer varies by menopausal status. Weight control may reduce the risk among postmenopausal women. *Am J Epidemiol* 2000;152:514–27.

body height; body weight; breast neoplasms; prospective studies

The relation between body size and breast cancer risk has been the subject of numerous investigations. Many of these studies have been focused on the association between weight (typically corrected for height) and breast cancer. Attention to the relation with height has increased in recent years due to increased interest in the effects of early diet on breast cancer risk in later life (1); adult height may serve as an indicator of childhood or adolescent nutrition and energy balance (2). Studies have revealed that associations with body size may vary by menopausal status. Hunter and Willett (3) concluded that for body mass index (BMI, defined as weight (kg)/height^2 (m^2)), most large case-control studies, but only some cohort studies, showed a clear positive association with postmenopausal breast cancer risk and that the relative risks found in cohort studies were much closer to the null value than were those from case-control studies. On the other hand, inverse associations with BMI were found for premenopausal breast cancer in most cohort studies, whereas case-control studies showed both inverse and direct associations (3, 4). For adult height, a modest positive association with breast cancer risk was found in most, but not all, case-control studies. These positive associations were predominantly found for postmenopausal breast cancer. Cohort studies have shown positive associa-

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Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; IGF, insulin-like growth factor; RR, relative risk.

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tions with height in both pre- and postmenopausal women (3), but several used databases in which information on height, but not reproductive and other risk factors, was available, leaving open the possibility of uncontrolled confounding.

Against this background, we studied the relation between height, weight, and BMI and breast cancer risk in the Pooling Project of Diet and Cancer (5). In this project, primary data from seven major prospective studies have been combined to evaluate associations between dietary factors and breast cancer risk by using a standardized approach. Since these studies also provided information on anthropometry and many covariates that can act as confounders or effect modifiers (e.g., reproductive factors, family history of cancer, and exogenous hormone use), we decided to use the pooled data for the current analysis of anthropometry and breast cancer as well. The pooling approach enables use of uniform categories of anthropometric variables and covariates and evaluation of potential effect modification by covariates.

MATERIALS AND METHODS

The Pooling Project has been described previously (5). Briefly, seven prospective studies (6–12) (table 1) were identified in 1992 that met the following predefined criteria: the study 1) had at least 200 incident cases of breast cancer available for analysis; 2) assessed long-term intake of foods and nutrients, including energy intake, at baseline; and 3) completed a validation study of the diet assessment method or a closely related instrument. For Pooling Project analyses (5), the Nurses' Health Study was split into two studies since it had repeated assessments of dietary intake and a longer follow-up period than did the other studies. To make the length of follow-up more comparable with the other cohorts, Nurses' Health Study (a) corresponds to the 1980–1986 follow-up period, while Nurses' Health Study (b) corresponds to the period 1986–1991. Self-administered questionnaires were used to assess anthropometric factors, reproductive factors, medical history, and family history. Each study measured dietary intake by using food frequency questionnaires. Incident breast cancers were ascertained by using follow-up questionnaires and inspection of medical records and/or tumor registry linkage. In all cohorts, follow-up was estimated to be more than 90 percent complete.

The questionnaires yielded self-reported information on height and weight at baseline. Weight at ages other than baseline age was not available for most cohorts; therefore, these variables and weight change could not be taken into account in this analysis. All height and weight data were converted into meters and kilograms, respectively. BMI (Quetelet index) was used as an indicator of relative weight. The correlation coefficients between height and BMI varied from −0.05 in the Nurses' Health Study to −0.13 in the Netherlands Cohort Study and the New York State Cohort.

Participants were excluded from these analyses if they met study-specific exclusion criteria, if their reported energy intake was greater than three standard deviations from the study-specific $\log_e$-transformed mean energy intake of the baseline population, if they reported a history of cancer other than nonmelanoma skin cancer at baseline, or if they had missing data on anthropometry. As a result of these additional exclusions and expanded follow-up in some studies, the baseline cohort size and the number of cases reported in these analyses may differ from original study-specific publications (7, 10, 13–15) and from previously reported Pooling Project publications (5, 16). The pooled analysis of anthropometry and breast cancer is based on 4,385 incident cases of invasive breast cancer (table 1).

Risk factors, including anthropometric factors, may differ for premenopausal and postmenopausal breast cancer (3). However, most of the cohort studies included had information on menopausal status at baseline only. As has been described before (16), to assign changing menopause status

TABLE 1. Characteristics of the cohort studies included in the pooled analysis of anthropometry and breast cancer, the Pooling Project of Diet and Cancer

Study	Baseline cohort size	Age at baseline (years)		Years of follow-up	No. of cases*		
		Median	Range		Total	Pre-menopausal	Post-menopausal
AHS†	15,172	52	28–90	1976–1982	122	20	87
CBSS†	56,837	50	40–59	1982–1987	392	122	242
IWHS†	34,406	61	55–69	1986–1991	643	0	643
NLCS†	62,412	61	55–69	1986–1989	420	0	420
NYSC†	18,475	68	50–93	1980–1987	358	0	358
NHS(a)†	89,046	47	34–59	1980–1986	1,015	383	571
NHS(b)†	68,817	53	40–65	1986–1991	787	130	613
SMC†	61,471	52	40–76	1987–1993	648	68	274
Total	337,819				4,385	723	3,208

* Cases consisted of women diagnosed with invasive breast cancer, with complete data on height and weight. A total of 454 cases were considered to have uncertain menopausal status at diagnosis (see text for details).

† AHS, Adventist Health Study; CBSS, Canadian National Breast Screening Study; IWHS, Iowa Women's Health Study; NLCS, Netherlands Cohort Study; NYSC, New York State Cohort; NHS(a), Nurses' Health Study (a); NHS(b), Nurses' Health Study (b); SMC, Sweden Mammography Cohort.

TABLE 3. **Study-specific and pooled multivariate relative risks* of breast cancer for continuous linear effects of height, weight, and body mass index, the Pooling Project of Diet and Cancer**

Anthropometric variable	AHS† RR 95% CI	CBSS† RR 95% CI	IWHS† RR 95% CI	NLCS† RR 95% CI	NYSC† RR 95% CI	NHS(a)† RR 95% CI	NHS(b)† RR 95% CI	SMC† RR 95% CI	Pooled RR† 95% CI†	p value, test for heterogeneity between studies
Height (5-cm increment)										
Premenopausal	—‡	0.98	—	—	—	1.05	0.97	0.98	1.02	0.74
		0.75, 1.28				0.97, 1.15	0.83, 1.12	0.78, 1.23	0.96, 1.10	
Postmenopausal	1.10	0.99	1.10	1.20	1.00	1.04	1.07	1.09	1.07	0.17
	0.91, 1.32	0.85, 1.16	1.03, 1.17	1.09, 1.32	0.92, 1.09	0.97, 1.12	1.00, 1.15	0.97, 1.23	1.03, 1.12	
Weight§ (10-kg increment)										
Premenopausal	—‡	0.86	—	—	—	0.87	0.95	0.93	0.90	0.80
		0.60, 1.22				0.79, 0.97	0.82, 1.11	0.66, 1.30	0.83, 0.97	
Postmenopausal	1.18	1.11	1.11	1.03	1.04	1.01	1.03	1.15	1.06	0.36
	0.97, 1.44	0.91, 1.36	1.04, 1.18	0.91, 1.16	0.95, 1.15	0.93, 1.09	0.97, 1.11	1.02, 1.30	1.03, 1.10	
Body mass index (4 kg/m^2 increment)										
Premenopausal	—‡	0.86	—	—	—	0.86	0.95	0.90	0.89	0.82
		0.60, 1.25				0.77, 0.96	0.80, 1.12	0.62, 1.32	0.81, 0.97	
Postmenopausal	1.21	1.11	1.11	0.99	1.05	1.01	1.04	1.15	1.07	0.34
	0.98, 1.50	0.91, 1.36	1.04, 1.19	0.86, 1.13	0.95, 1.16	0.93, 1.10	0.97, 1.12	1.01, 1.32	1.02, 1.11	

* Relative risks were adjusted for age at menarche (≤11, 12, 13, 14, ≥15 years), parity (0, 1, 2, ≥3), age at birth of the first child (≤20, 21–25, 26, 30, ≥30 years), postmenopausal hormone use (ever, never), oral contraceptive use (ever, never), history of benign breast disease (no, yes), maternal history of breast cancer (no, yes), history of breast cancer in a sister (no, yes, no sisters), smoking status (ever, never), education (less than high school graduation, high school graduation, more than high school graduation), fat intake (quintiles), fiber intake (quintiles), energy intake (continuous), and alcohol intake (0, >0–<1.5, 1.5–<5, 5–<15, 15–<30, ≥30 g/day).

† AHS, Adventist Health Study; CBSS, Canadian National Breast Screening Study; IWHS, Iowa Women's Health Study; NLCS, Netherlands Cohort Study; NYSC, New York State Cohort; NHS(a), Nurses' Health Study (a); NHS(b), Nurses' Health Study (b); SMC, Sweden Mammography Cohort; RR, relative risk; CI, confidence interval.

‡ The Adventist Health Study was not included in analyses of premenopausal women.

§ Further adjusted for height.

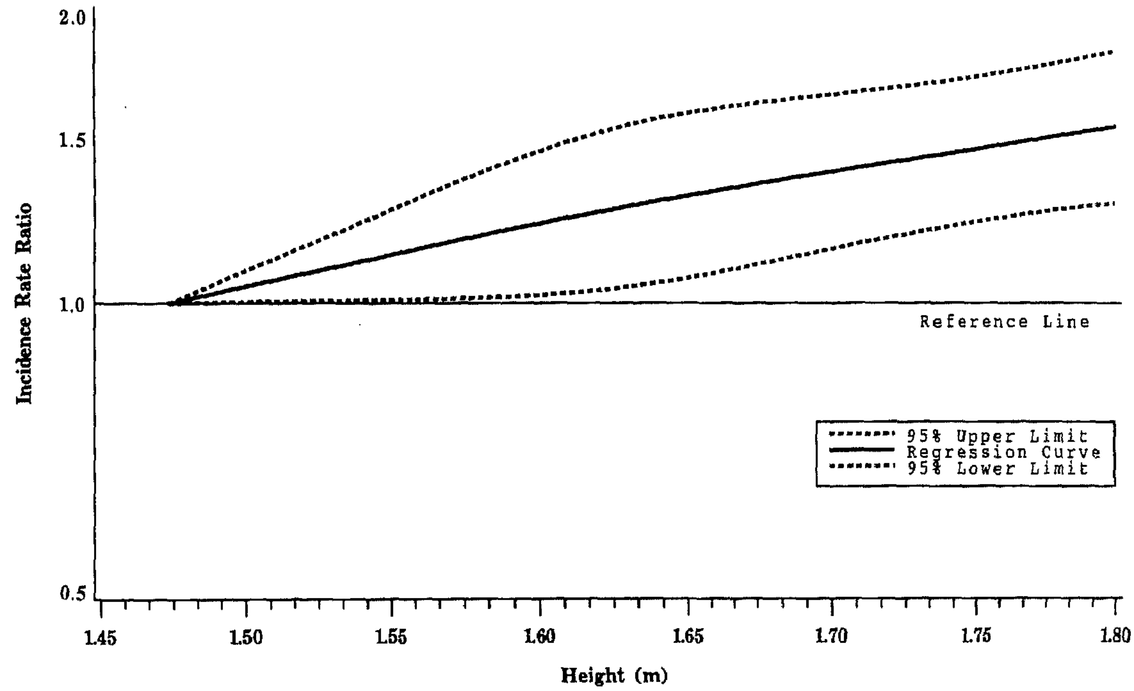

FIGURE 1. Nonparametric regression curve for the relation between height and breast cancer, the Pooling Project of Diet and Cancer.

linearity was also not significant ($p = 0.65$). The results for BMI are shown in figure 2 for pre- and postmenopausal women separately. Although the test for deviation from linearity in premenopausal women was technically not significant ($p = 0.06$), power was limited due to small numbers in this group. Among postmenopausal women, there was significant deviation from linearity ($p = 0.004$). The curve among postmenopausal women suggests that the relative risk did not increase further above BMI of more than 28 kg/m^2. When BMI more than 28 kg/m^2 was used as the highest category in the categorical analyses, the RR was 1.26 (95 percent CI: 1.09, 1.46) (data not shown).

The results of the analyses on interaction are given in tables 4 and 5. In these analyses, height and BMI were entered as continuous variables into the models, and relative risks for these variables were estimated in each category of the covariates. The analysis by menopausal status (table 4) showed no evidence for interaction between menopausal status and height (p value, test for interaction = 0.13), but there was significant interaction with BMI (p value, test for interaction = 0.004). Therefore, in the ensuing analyses, interactions with height were evaluated in the total group, whereas interactions with BMI were evaluated in pre- and postmenopausal women separately. Before further evaluation of interactions with other covariates, the mutual interaction between height and BMI was considered. As table 4 shows, the effect of height was not significantly different between BMI categories, nor was the effect of BMI significantly different between height categories in the pre- and postmenopausal women. When the breast cancer associations with height and BMI were evaluated according to categories of age at diagnosis, the association with height and BMI appeared to be somewhat stronger in older, postmenopausal women. In premenopausal women, the association with BMI was more inverse in older premenopausal women. However, the interactions with age at diagnosis were not significant in either pre- or postmenopausal women (table 4).

Table 5 shows results of interaction analyses for other covariates. No significant interactions with height or BMI on breast cancer risk were found except for the interaction between a maternal history of breast cancer and height. Women with a maternal history of breast cancer had a pooled RR of 1.23 per height increment of 5 cm, whereas women without such a history had a pooled RR of 1.07. This interaction was noted in every cohort except the Sweden Mammography Cohort. However, the association with height was opposite (although not significant) in those with a history of breast cancer in a sister, which was consistent across the cohorts. The association of BMI and breast cancer among premenopausal women also showed variation according to the history of breast cancer in a sister. Although the same pattern occurred in every cohort, this interaction was not significant. No interactions were seen between overall family history of breast cancer and height or BMI (data not shown). For height, a borderline significant interaction was seen with a history of benign breast disease, which was apparent in every cohort except the Sweden Mammography Cohort. Although the interaction was not significant, it is of interest, given the possible role of estro-

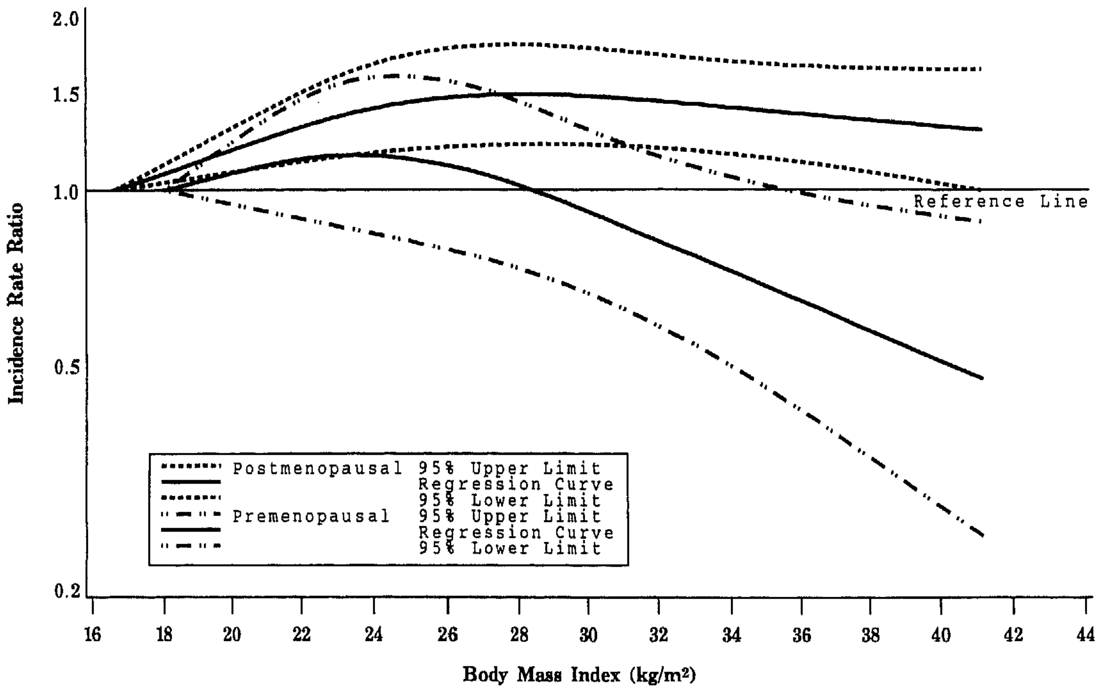

FIGURE 2. Nonparametric regression curve for the relation between body mass index and breast cancer, the Pooling Project of Diet and Cancer.

gens in the etiology of breast cancer, that the association between BMI and breast cancer was stronger and was significant only among women who never used postmenopausal hormone replacement therapy (HRT). There was also a tendency for the association between BMI and breast cancer in postmenopausal women to decrease with increasing alcohol intake. Analyses with categorical BMI (<21, 21–<25, 25–<28, and ≥28 kg/m^2) in the model revealed the same pattern of interaction with age at diagnosis, HRT use, and alcohol as was observed with continuous BMI in postmenopausal women (data not shown).

DISCUSSION

In this pooled analysis of seven major prospective cohort studies on risk factors for breast cancer, we found a significant positive association between height and the risk of postmenopausal breast cancer. In premenopausal women, the association was less clear and was not significant, and the interaction by menopausal status was not significant. Weight and BMI showed significant inverse associations with risk of premenopausal breast cancer and significant positive associations with postmenopausal breast cancer. This interaction by menopausal status was highly significant. There was no statistically significant heterogeneity among the studies for these associations. The associations of these anthropometric factors were independent of other risk factors for breast cancer and were not significantly modified by most of these factors, except for a possible interaction between height and maternal history of breast cancer.

The studies we used are a subset of prospective studies on anthropometric factors and breast cancer risk, but represent all studies with data on food and nutrient intakes that could potentially confound the anthropometric associations. The Pooling Project includes cohort studies with detailed dietary data and other relevant breast cancer risk factors. Because, in the current analysis of anthropometric indices and breast cancer, we wanted to be able to adjust for possible confounding by both nondietary and dietary risk factors, we decided to use the originally collected pooled data set. For example, alcohol intake is a risk factor for breast cancer (16), which also may be associated with BMI. Our pooling results regarding height are in agreement with results of major cohort studies not included that lack reproductive or dietary data (22–24). For BMI, the results among premenopausal women are also comparable (22, 24), but less so in postmenopausal women (24). The availability of information on many potential confounders is a major strength of our pooled analysis to rule out confounding bias, and it also provides an opportunity to examine potential effect modification. A disadvantage is that our analysis of premenopausal breast cancer was based on only four cohorts. Although this comprised over 700 premenopausal cases, the estimates were clearly less precise than were those for postmenopausal women.

Another potential drawback of this analysis is the use of self-reported data on height and weight in our cohort studies. Although some attenuation of relative risk estimates might have occurred because of imperfect measurements, the potential for bias is small, considering that validation studies of self-reported measurements show high correla-

TABLE 4. Pooled multivariate relative risks* (95% confidence intervals) for a 5-cm increment in height and a 4-kg/m² increment in body mass index by menopausal status, anthropometric factors, and age at diagnosis†, the Pooling Project of Diet and Cancer

Covariate and anthropometric variable	Category of covariate					p value, test for interaction
Menopausal status‡	Premenopausal	Postmenopausal				
Height	1.02 (0.96, 1.10)	1.07 (1.03, 1.12)				0.13
BMI§	0.89 (0.81, 0.97)	1.07 (1.02, 1.11)				0.004
BMI (kg/m²)	<21	21–<23	23–<25	25–<29	≥29	
Height	1.10 (1.02, 1.17)	1.08 (0.98, 1.19)	1.09 (1.03, 1.15)	1.08 (1.03, 1.14)	1.02 (0.93, 1.12)	0.12
Height (m)	<1.60	1.60–<1.65	1.65–<1.70	1.70–<1.75	≥1.75	
BMI						
Premenopausal	0.85 (0.62, 1.17)	0.92 (0.79, 1.07)	0.94 (0.81, 1.09)	0.87 (0.70, 1.08)	0.93 (0.64, 1.36)	0.40
Postmenopausal	1.10 (1.03, 1.18)	1.10 (1.02, 1.18)	1.06 (0.99, 1.14)	1.02 (0.92, 1.12)	1.02 (0.81, 1.29)	0.30
Age at diagnosis (years)‡ in premenopausal women	<45	45–<50	>50			
Height	0.98 (0.80, 1.20)	1.06 (0.95, 1.17)	1.01 (0.85, 1.21)			0.70
BMI	1.04 (0.74, 1.46)	0.95 (0.84, 1.08)	0.73 (0.54, 0.98)			0.08
Age at diagnosis (years) in postmenopausal women	<55	55–<60	60–<65	65–<70	≥70	
Height	1.12 (1.00, 1.26)	1.06 (0.95, 1.18)	1.04 (0.94, 1.16)	1.14 (1.06, 1.23)	1.15 (1.02, 1.30)	0.24
BMI	0.97 (0.86, 1.10)	1.04 (0.94, 1.16)	1.06 (0.95, 1.17)	1.15 (1.07, 1.24)	1.09 (0.99, 1.20)	0.13

* Relative risks were adjusted for age at menarche (≤11, 12, 13, 14, ≥15 years), parity (0, 1, 2, ≥3), age at birth of the first child (≤20, 21–25, 26–30, ≥30 years), postmenopausal hormone use (ever, never), oral contraceptive use (ever, never), history of benign breast disease (no, yes), maternal history of breast cancer (no, yes), history of breast cancer in a sister (no, yes, no sisters), smoking status (ever, never), education (less than high school graduation, high school graduation, more than high school graduation), fat intake (quintiles), fiber intake (quintiles), energy intake (continuous), and alcohol intake (0, >0–<1.5, 1.5–<5, 5–<15, 15–<30, ≥30 g/day).

† The Adventist Health Study was not included in all analyses of premenopausal women.

‡ The Iowa Women's Health Study, the Netherlands Cohort Study, and the New York State Cohort were not included in this analysis.

§ BMI, body mass index.

tions ($r > 0.8$) with measured anthropometric data (25–27), and all data here were reported prior to the occurrence of outcomes. Furthermore, various prospective studies in which height and weight were actually measured (e.g., 22, 24, 28, 29) generally reported associations between height, weight, and breast cancer that were consistent with those from prospective studies relying on self-reported data. Selection bias due to incomplete follow-up is unlikely because all cohorts show high degrees of completeness of follow-up.

Height and breast cancer

A positive association between attained height and breast cancer risk has been found in many earlier studies (3). The positive association with height was less clear for premenopausal than for postmenopausal breast cancer in large (>500 cases) case-control studies (3), but recent, large case-control studies showed comparable positive associations in both menopausal strata (30–34). Two other recent, large case-control studies reported no association in pre- or postmenopausal women (35, 36), but others reported a significant positive association among young premenopausal women (37).

Most cohort studies (13, 15, 23, 24, 28, 29, 38–40), but not all (41–43), reported a positive association between height and breast cancer. Several of these studies were able to compare menopausal strata and reported weaker associations among premenopausal women (13, 24, 29, 38). Our pooled analysis showed an overall positive association with premenopausal breast cancer, but the effect was less clear than that in postmenopausal cases and showed more variability among studies.

In our analysis of effect modification of height and breast cancer, we found a significant interaction only with a maternal history of breast cancer, with a much stronger association among women with a positive maternal history. Although this is in agreement with earlier findings regarding overall family history of breast cancer (44, 45), it is not consistent with our opposite finding of a lower degree of risk among women with a sister with breast cancer. The directions of the effect modification were quite consistent across the cohorts, suggesting that these interactions may not be due to chance. These interactions merit further attention.

TABLE 5. Pooled multivariate relative risks* (95% confidence intervals) for a 5-cm increment in height and a 4-kg/m² increment in body mass index by levels of nondietary and dietary factors†, the Pooling Project of Diet and Cancer

Covariate and anthropometric variable	Category of covariate					p value, test for interaction
Age at menarche (years)‡	<12	12	13	14	≥15	
Height	1.03 (0.92, 1.15)	1.12 (1.01, 1.24)	1.03 (0.97, 1.08)	1.13 (1.01, 1.26)	1.07 (0.99, 1.17)	0.70
BMI						
Premenopausal	0.88 (0.72, 1.09)	1.00 (0.87, 1.16)	0.84 (0.60, 1.17)	0.89 (0.64, 1.24)	0.94 (0.66, 1.35)	0.94
Postmenopausal	1.07 (0.99, 1.16)	1.07 (1.00, 1.16)	1.05 (0.98, 1.13)	1.05 (0.94, 1.18)	1.11 (0.96, 1.29)	0.77
Parity	0	1–2	≥3			
Height	1.05 (0.97, 1.15)	1.08 (1.02, 1.15)	1.06 (1.02, 1.11)			0.89
BMI						
Premenopausal	0.98 (0.58, 1.66)	0.85 (0.71, 1.02)	0.93 (0.82, 1.05)			0.76
Postmenopausal	1.08 (0.99, 1.19)	1.11 (1.02, 1.20)	1.03 (0.98, 1.08)			0.23
Age at first birth (years)	≤20	>20–25	>25–30	>30		
Height	1.07 (0.94, 1.22)	1.07 (1.03, 1.12)	1.07 (1.01, 1.13)	1.05 (0.96, 1.14)		0.54
BMI						
Premenopausal	0.89 (0.64, 1.25)	0.94 (0.75, 1.17)	0.89 (0.75, 1.05)	0.87 (0.60, 1.25)		0.99
Postmenopausal	1.06 (0.96, 1.18)	1.07 (1.01, 1.13)	1.10 (1.00, 1.21)	0.98 (0.86, 1.12)		0.86
Benign breast disease‡	No	Yes				
Height	1.10 (1.05, 1.15)	1.02 (0.97, 1.09)				0.06
BMI						
Premenopausal	0.87 (0.78, 0.96)	0.95 (0.69, 1.33)				0.60
Postmenopausal	1.06 (1.00, 1.12)	1.07 (0.97, 1.17)				0.82
Maternal history of breast cancer‡	No	Yes				
Height	1.07 (1.02, 1.12)	1.23 (1.11, 1.37)				0.005
BMI						
Premenopausal	0.87 (0.79, 0.97)	0.78 (0.46, 1.34)				0.64
Postmenopausal	1.07 (1.01, 1.13)	1.08 (0.95, 1.24)				0.77
History of breast cancer in a sister‡	No	Yes				
Height	1.07 (1.02, 1.12)	0.96 (0.85, 1.09)				0.08
BMI						
Premenopausal	0.82 (0.73, 0.92)	1.88 (0.63, 5.61)				0.14
Postmenopausal	1.07 (1.03, 1.12)	1.08 (0.93, 1.26)				1.00
Oral contraceptive use‡	Never	Ever				
Height	1.09 (1.04, 1.15)	1.03 (0.98, 1.09)				0.21
BMI						
Premenopausal	0.85 (0.73, 0.98)	0.91 (0.82, 1.02)				0.44
Postmenopausal	1.08 (1.01, 1.16)	1.06 (0.95, 1.19)				0.97

Table continues

Because attained height might be an indicator of childhood energy intake in situations in which there is sufficient variation in energy intake (2), this has been proposed as an explanation for the observation that the positive association between height and breast cancer was found more frequently in European populations that experienced food shortages during World War II (13, 24). Indeed, stronger associations have generally been found in studies of the affected birth cohorts in Norway, the Channel Islands, and the Netherlands, where severe food deprivation occurred at the end of the War (15, 24, 29, 40) compared with US cohort studies (3). It is also consistent with the prior observations that associations were found in US Black women (33) as opposed to White women (36) and in US cohorts with overrepresentation of women potentially undernourished during childhood or adolescence (28), as well as with many animal studies showing that energy restriction clearly reduces experimentally induced and spontaneous mammary tumor risk in rodents (46). However, more recent studies show that height is also rather consistently related to breast cancer risk

TABLE 5. Continued

Covariate and anthropometric variable	Category of covariate					p value, test for interaction
Hormone replacement therapy use‡	Never	Ever				
Height (postmenopausal)	1.06 (1.00, 1.13)	1.09 (1.03, 1.15)				0.45
BMI (postmenopausal)	1.09 (1.04, 1.14)	1.04 (0.92, 1.18)				0.24
Education§	Less than high school	High school	More than high school			
Height	1.10 (1.04, 1.17)	1.11 (1.02, 1.20)	1.00 (0.93, 1.08)			0.28
BMI						
Premenopausal	0.89 (0.62, 1.27)	0.66 (0.31, 1.41)	1.28 (0.85, 1.93)			0.17
Postmenopausal	1.12 (0.99, 1.25)	1.04 (0.93, 1.16)	1.08 (0.99, 1.17)			0.37
Dietary fiber intake	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Height	1.09 (1.02, 1.17)	1.01 (0.95, 1.07)	1.10 (1.03, 1.16)	1.11 (1.02, 1.21)	1.03 (0.97, 1.09)	0.84
BMI						
Premenopausal	0.85 (0.60, 1.19)	0.86 (0.70, 1.04)	0.89 (0.72, 1.10)	0.95 (0.80, 1.13)	1.00 (0.78, 1.28)	0.34
Postmenopausal	1.09 (1.01, 1.18)	1.04 (0.93, 1.17)	1.01 (0.93, 1.11)	1.05 (0.95, 1.17)	1.13 (1.03, 1.23)	0.52
Total fat intake	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Height	1.01 (0.95, 1.08)	1.08 (1.02, 1.15)	1.11 (1.05, 1.18)	1.04 (0.98, 1.11)	1.07 (0.99, 1.15)	0.31
BMI						
Premenopausal	0.86 (0.70, 1.05)	0.77 (0.62, 0.96)	0.90 (0.73, 1.11)	0.95 (0.78, 1.16)	0.96 (0.82, 1.12)	0.14
Postmenopausal	1.10 (0.98, 1.24)	1.07 (0.99, 1.16)	0.99 (0.92, 1.07)	1.10 (1.00, 1.20)	1.08 (0.97, 1.20)	0.93
Alcohol intake (g/day)	0	1–<30	≥30			
Height	1.08 (1.03, 1.13)	1.05 (1.00, 1.12)	1.06 (0.94, 1.19)			0.76
BMI						
Premenopausal	0.89 (0.77, 1.02)	0.93 (0.75, 1.14)	0.92 (0.57, 1.49)			0.92
Postmenopausal	1.07 (1.02, 1.13)	1.04 (0.99, 1.10)	1.00 (0.75, 1.35)			0.78
Smoking¶	Never	Ever				
Height	1.05 (1.00, 1.11)	1.07 (0.99, 1.16)				0.56
BMI						
Premenopausal	0.89 (0.78, 1.01)	0.88 (0.78, 1.00)				0.94
Postmenopausal	1.05 (1.00, 1.10)	1.06 (1.00, 1.14)				0.39

* Relative risks were adjusted for age at menarche (≤11, 12, 13, 14, ≥15 years), parity (0, 1, 2, ≥3), age at birth of the first child (≤20, 21–25, 26–30, >30 years), postmenopausal hormone use (ever, never), oral contraceptive use (ever, never), history of benign breast disease (no, yes), maternal history of breast cancer (no, yes), history of breast cancer in a sister (no, yes, no sisters), smoking status (ever, never), education (less than high school graduation, high school graduation, more than high school graduation), fat intake (quintiles), fiber intake (quintiles), energy intake (continuous), and alcohol intake (0, >0–<1.5, 1.5–<5, 5–<15, 15–<30, ≥30 g/day).

† The Adventist Health Study was not included in analyses of premenopausal women.

‡ The New York State Cohort was not included in this analysis.

§ The Nurses' Health Studies (a) and (b) were not included in this analysis.

¶ The Sweden Mammography Cohort was not included in this analysis.

in relatively affluent populations that have not experienced energy restriction during growth periods and in which height is presumably primarily genetically determined (30, 31, 37, 47). It has also been hypothesized that height reflects mammary gland mass (or more precisely, the number of ductal stem cells that develop in the breast in utero), which could be related to breast cancer risk (48).

Considering that nutritional inadequacy does not seem to be the only factor responsible for the association between height and breast cancer, Ballard-Barbash (45) has proposed that genetic and environmental factors (e.g., diet and physical activity) may affect the hormones that influence epiphyseal closure during puberty and, thus, attained height. Furthermore, Stoll (49) has suggested that better nutrition accelerates growth hormone release which, in turn, increases levels of insulin-like growth factor (IGF). The adolescent growth spurt involves stimulation by growth hormone, insulin, IGF, and sex steroids, and Stoll hypothesizes that the combination of IGF and sex steroids results in mitogenic effects on developing mammary tissue in adolescence and a concomitant increased risk of epithelial atypia and carcinogenesis. This is compatible with the observation (50) that plasma levels of IGF-1 predicted the incidence of premenopausal, but not postmenopausal, breast cancer. Dorgan et al. (51) have suggested, on the basis of a cross-sectional study, that height might influence breast cancer risk through its positive association with follicular-phase plasma estradiol.

Weight and premenopausal breast cancer

Our findings of an inverse association between relative weight and premenopausal breast cancer confirm those of most earlier studies in Western, high-risk countries (13, 30, 31, 35, 37, 52–61). Ziegler et al. (34) also recently reported a decreased risk among heavy, young (age <40 years) women in a case-control study among Asian-American women living in the western United States. In our pooled analysis, the strongest inverse associations were found for women with a BMI of more than 31 kg/m^2. There was no significant heterogeneity between the studies in this respect. Earlier reports also showed that the inverse association is frequently limited to the higher relative weight categories but, due to the differences in relative weight distributions and the widely differing categorizations that were used, no clear cutoff value for BMI has emerged above which there is a decreased breast cancer risk. For example, significantly decreased relative risks have been reported for women with a BMI of more than 21 (13), more than 22 (37), more than 28.8 (35), and 30 kg/m^2 or more (62). When we used an upper BMI category of 29 kg/m^2 or more, we also found a significantly decreased risk of 0.68 (95 percent CI: 0.48, 0.97) (data not shown). However, our extended analyses indicated that the inverse association is limited mainly to women with a BMI of 31 kg/m^2 or more. Thus, although there seems to be no uniformity in the literature regarding a BMI value above which breast cancer risk decreases, the overall inverse association as such is a rather consistent finding in cohort studies and also in recent case-control studies, particularly among younger premenopausal women (30, 34, 35, 37, 63).

In spite of this consistency, explanations for this finding are far from satisfactory. Detection bias could be responsible for this effect, but this was concluded to be unlikely (31, 46, 64, 65). Pathak and Whittemore (58) compared countries with high, medium, and low breast cancer risk and concluded that it is unlikely that detection of breast cancer would be masked by obesity in high-risk countries and not in medium-risk populations, where positive associations with relative weight have been found. The inverse association in case-control studies also is not likely to be due to disease or treatment effects (37).

It has been proposed that, in premenopausal women, obesity may protect against breast cancer by causing more frequent anovulatory menstrual cycles (66, 67). This would result in decreased estradiol and progesterone levels and lower luteal phase progesterone levels in ovulatory cycles (68). However, the level of obesity needed to induce sufficient anovulatory cycles so that breast cancer risk is decreased is unclear (69). Interestingly, the association with BMI was somewhat less strong among women who had ever used oral contraceptives and had thus experienced anovulatory cycles due to oral contraceptive use. Swanson et al. (37) reported that irregularity of menstrual cycles, as a crude indicator of anovulatory cycles, could not explain the reduced breast cancer risk among obese women. Few population-based studies have looked at the relation between BMI and menstrual cycle length or variability or bleeding patterns (70–74). In Nurses Health Study II, a U-shaped relation between BMI and menstrual irregularity was observed, with most regularity between a BMI of 18 and 22 kg/m^2 (74). In the same study, both short and long/irregular cycles were associated with reduced breast cancer risk (75). Because the pooled cohorts have few women with a BMI of less than 18 kg/m^2, the inverse association here is seen only in high BMI categories, which supports the hypothesis that more anovulatory cycles lead to reduced premenopausal breast cancer risk.

As shown before (66), Potishman et al. (76) found that sex hormone-binding globulin levels decreased with increasing BMI in both pre- and postmenopausal women. However, with increasing BMI, total estradiol concentrations decreased in premenopausal women, but increased in postmenopausal women. They propose that lower estradiol levels in premenopausal, obese women are the result of increased estradiol clearance due to reduced serum-hormone binding capacity.

Weight and postmenopausal breast cancer

The significant positive association between relative weight and postmenopausal breast cancer in this pooled analysis is consistent with results of many case-control studies (3). Cohort studies have often shown weak positive or no associations among postmenopausal women (13–15, 22, 23, 29, 39, 42, 43), although significant positive associations have also been reported (24, 47, 63). Our current results, combining several of the above studies plus additional cohorts, show a modest, significantly positive association. Although no association was seen in two cohorts (Netherlands Cohort Study and Nurses' Health Study (a)), no statistically significant heterogeneity was observed in this pooled analysis. Several studies indicate that the relation between relative weight and breast cancer risk might be stronger in older postmenopausal women (35, 63). In our current analysis, we saw no significant effect modification by age at diagnosis, but there was some suggestion that women older than age 65 years at diagnosis showed stronger associations with BMI than did younger women. Since most published cohort studies have not included large numbers of older women, this interaction may become more apparent as the cohorts mature.

Fat distribution has been proposed as more predictive of breast cancer risk than is body mass (59, 77). However, waist-to-hip circumference ratio as a measure of abdominal obesity or other indices of fat distribution has not been consistently associated with breast cancer risk (14, 35, 77). In postmenopausal women, ovarian estrogen production is diminished, and estrogen, which may promote tumor growth, is derived mainly from the aromatization of androstenedione that occurs primarily in adipose tissue. Perhaps high estrogen levels could occur near breast adipose tissue (34). Furthermore, excess weight is associated with decreased sex hormone-binding globulin levels (78), resulting in increased levels of biologically active estrogens (45). Higher levels of estrone and estradiol have been found in obese postmenopausal women compared with women of normal weight (79, 80). An upper threshold for the effect of BMI, such as we observed above 28 kg/m^2, is also consistent with estrogen receptor-mediated effects.

Our results on potential effect modification by HRT of the association between BMI and postmenopausal breast cancer are in accordance with the elevated extraovarian estrogen hypothesis. Although no significant interaction was noted, possibly due to lack of update of HRT use in most cohorts, the BMI-breast cancer association was stronger and was significant only among women who never had used HRT, i.e., among women in whom estrogen exposure is determined only by endogenous estrogen production. Recently, Huang et al. (81) reported a similar interaction between BMI and HRT, which was statistically significant. Moderately strong positive associations between plasma estrogen levels and postmenopausal breast cancer risk have been reported recently (82), especially in nonusers of HRT. Alcohol intake is positively associated with risk of breast cancer (16), possibly through elevation of estrogen levels. As with HRT as exogenous source of estrogens, the BMI-breast cancer association was diminished in alcohol drinkers and was significant only among nondrinkers in our pooled analysis, although the interaction was not significant. In contrast to an earlier report (44), we observed no indication that family history of breast cancer modifies the relation between BMI and postmenopausal breast cancer risk, as was also found recently by others (30).

In conclusion, this study, based on over 4,000 incident breast cancer cases, provides further evidence of a modest positive association between adult height and breast cancer, suggesting a possible etiologic role for factors (including diet) operating in early life on breast cancer risk later in life. This study also provides further evidence for moderate inverse and positive trends in breast cancer risk associated with relative weight in pre- and postmenopausal breast cancer, respectively. Further research is warranted regarding the timing of the change in direction of the effect of excess weight in relation to a woman's age. Because weight is one of the few modifiable breast cancer risk factors, weight control provides an important opportunity for prevention of postmenopausal breast cancer.

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